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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/869,869	07/06/2001	Stuart J. Knechtle	14028.0293U1	1262

23859 7590 09/14/2005

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EXAMINER	
GAMBEL, PHILLIP	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 09/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/869,869	KNECHTLE ET AL.	
	Examiner	Art Unit	
	Phillip Gambel	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 July 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-33* is/are pending in the application.

4a) Of the above claim(s) *14-20 and 29-33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13 and 21-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____. APPLICANT ACKNOWLEDGED IDS FILED 7/1/05 BELONGS TO IN STANT APPLICATION PG
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

SRD

Detailed Action

1. Applicant's amendment, filed 7/1/05, has been entered.

Applicant's election with traverse Group I and the provisional election of species (i) CTLA4-Ig and anti-CD3 immuntoxin has been acknowledged.

As pointed out previously, claims 1-13 and 21-28 are being examined to the extent that the methods reads on methods of preventing chronic rejection of a transplant by administering anti-CD3 immunotoxin and CTLA4.

Claims 14-20 and 29-33 have been withdrawn from consideration as being drawn to non-elected Groups or species.

2. The text of those sections of Title 35 USC not included in this Action can be found in a prior Action.
This Action will be in response to applicant's arguments, filed 7/1/05.
The rejections of record can be found in the previous Office Action.

3. The previous objection to the lack of providing an Abstract of the disclosure as required by 37 CFR 1.72(b) has been withdrawn in view of the filing of a 371 application.

4. Claim 10 stands rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention essentially for the reasons of record.

It is apparent that the UCHT1-CRM9 immunotoxin is required to practice the claimed invention. As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 USC 112, first paragraph, may be satisfied by a deposit of the cell line which produces this immunotoxin. See 37 CFR 1.801-1.809.

In addition to the conditions under the Budapest Treaty, applicant is required to satisfy that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent in U.S. patent applications.
Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.
If the original deposit is made after the effective filing date of an application for patent, the applicant should promptly submit a verified statement from a person in a position to corroborate the fact, and should state, that the biological material which is deposited is a biological material specifically identified in the application as filed, except if the person is an attorney or agent registered to practice before the Office, in which the case the statement need not be verified. See MPEP 1.804(b).

Alternatively, applicant again is invited to provide evidence that the conditions required for the biological materials under the deposit requirements under 35 USC 112, first paragraph, with respect to the claimed "UCHT1-CRM9 immunotoxin" have been satisfied.

Applicant's arguments, filed 7/1/05, have been fully considered but are not found convincing essentially for the reasons of record.

Applicant asserts that the claimed "UCHT1-CRM9 immunotoxin" was widely known and readily obtainable from publicly available material with only routine experimentation, by relying upon U.S. Patent Nos. 6,167,956 and 5,725,857 and PCT Publications WO 98/39425 and WO 98/39363 and incorporation by reference to these documents as well as several publications (Exhibits A and B).

However, biological materials must be known and readily available to the public (See MPEP 2404.01). Neither concept alone is sufficient.

The mere reference to a deposit or the biological material itself in any document or publication does not necessarily mean that the deposited biological material is readily available. Even a deposit made under the Budapest Treaty and references in a United States or foreign patent document would not necessarily meet the test for known and readily available unless the deposit was made under conditions that are consistent with those specified in these rules, including the provision that requires, with one possible exception (37 CFR 1.88(b)), that all restrictions on the accessibility be irrevocably removed by the applicant upon the granting of the patent.

The Office will accept commercial availability (if applicant is relying upon Oxoid USA) as evidence that a biological material is known and readily available only when the evidence is clear and convincing that the public has access to the material.

The fact that applicant and other members of the public were able to obtain the materials in question prior to and after the filing date of the application does not establish the upon issuance of a patent on the application that such material would continue to be accessible to the public.

The applicant did not make of record any of the facts and circumstances surrounding the access to the biological materials given applicant's reliance upon patents and publications, nor is there any evidence as any policies regarding the material if a patent would be granted.

Further, there is no assurance that the public will have unlimited access to the material if the application has matured into a patent. In the absence of evidence that the "UCHT1-CRM9 immunotoxin" is readily available to the public and that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent, applicant's arguments are not persuasive and the rejection is maintained.

Applicant's arguments have not been found persuasive.

5. Claim 10 stands rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention essentially for the reasons of record.

Claim 10 is indefinite in the recitation of "UCHT1-CRM9" because its characteristics are not known. The use of "UCHT1-CRM9" immunotoxin as the sole means of identifying the claimed antibody and biological molecule renders the claim indefinite because "UCHT1-CRM9" is merely a laboratory designation which does not clearly define the claimed product, since different laboratories may use the same laboratory designation s to define completely distinct biological materials or cell lines.

Amending the claims to recite the appropriate deposit Accession Number would obviate this rejection.

Applicant is reminded that the amendment must point to a basis in the specification so as not to add any new matter. See MPEP 714.02 and 2163.06

Applicant's arguments, filed 7/1/05, have been fully considered but are not found convincing.

Applicant's reliance upon the instant description on the immunotoxin CRM9, publications and the commercial availability of the UCHT1 antibody is acknowledged.

However, as noted above, applicant has not made of record any of the facts and circumstances surrounding the access to the biological materials given applicant's reliance upon patents, publications and commercial availability.

6. Claims 1-13 and 21-28 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Neville et al. (U.S. Patent No. 6,103,235) in view of Sykes et al. U.S. Patent No. 6,514,513) AND/OR Gray et al. (U.S. Patent No. 6,750,334) and in further view of Strom et al. (in Therapeutic Immunology, edited by Austen et al., Blackwell Science, Cambridge MA, 1996; pages 451-456) essentially for the reasons of record.

Applicant's arguments, filed 7/1/05, have been fully considered but are not found convincing.

Once a prima facie case of obviousness has been made the burden of going further is shifted to applicant. In re Keller, 208 USPQ 871, 882 (CCPA 1981). This applicant has not done, but rather argues the references individually and not their combination. One cannot show non-obviousness by attacking references individually where the rejections are based on a combination of references. In re Young 403 F.2d 759, 150 USPQ 725 (CCPA 1968). See MPEP 2145.

In response to applicant's arguments that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See In re Fine 5 USPQ2d 1596 (Fed. Cir 1988) and In re Jones 21 USPQ2d 1941 (Fed. Cir. 1992).

Therefore, it would have obvious to a person of ordinary skill in the art at the time the invention was made to combine the teachings of the references to reduce or eliminate T cell responses via a multitiered approach by combining anti-T cell immunotherapy, such as the anti-CD3 immuntoxins, taught by Neville et al., with a costimulatory inhibitor such as CTLA4Ig, as taught by Sykes and Gray et al., in order to target different targets and mechanisms of action to increase immunosuppression while decreasing the undesirable effects of immunosuppression therapy, including that which accompanies transplantation

In this case the teachings of the prior art (reiterated below for applicant's convenience) pertaining to the issues of inducing immune tolerance or immunological specific non-responsiveness to foreign mammalian donor organs cell also indicated success in the relevant combination therapy to solve a similar problem would have led one of ordinary skill in the art at the time the invention was made to combine the references to solve a well known problem in the art. The strongest rationale for combining reference is a recognition, expressly or implicitly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent that some advantage or expected beneficial result would have been produced by their combination In re Sernaker 17 USPQ 1, 5-6 (Fed. Cir. 1983) see MPEP 2144

The following is reiterated for applicant's convenience.

Neville et al. teach methods of inducing immune tolerance or immunological specific non-responsiveness to foreign mammalian donor organs cell (e.g. including live donors on column 8, paragraph 2 and column 9)

by safely exposing the recipient so as to reduce the recipient T cells with anti-CD3 immunotoxins, including the UCHT1-CRM9 / T cell CD3ε epitope –specific / divalent / diphtheria (e.g., see columns 4-10 of the Detailed Description of the Invention),

including administering known immunosuppressant such as those encompassed by the instant claims (e.g. see Method of Inducing Immune Tolerance, Methods of Treating Graft –Versus-Host Disease on columns 8-10, particularly column 8, paragraph 5 – column 9) (see entire document).

Neville et al. also teach modes of administering, including administering said immunotoxin prior to, during and following transplantation, wherein one skilled in the art can readily determine the particular treatment protocol and suitable amounts (e.g., see column 7, paragraph 2 – column 10).

Such methods present a significant opportunity to reduce or eliminate traditional immunosuppressant therapy and its well -documented negative side-effects (e.g. see column 9, paragraph 1).

Neville et al. differs from the instant methods by not describing the known costimulatory blockers such as CTLA4 / CTLA4-Ig in immunosuppressive regimens to promote graft survival.

Sykes teaches methods of inducing tolerance to foreign antigens, including heart, pancreas, liver and kidney (e.g. see column 8, paragraph 2) by promoting primate / human allograft acceptance by administering a costimulatory blocker, including CTLAIg (e.g. see column 9, paragraph 2-3)

including combination with T cell depletion or inactivation with anti-T cell antibodies (e.g. see column 9, paragraphs 6-8 and column 13, paragraphs 2-6).

Similar to Neville et al., Sykes teaches various modes of administration including providing immunosuppressive therapy multiple times prior to, during and after transplantation according to the needs of the patients (see Detailed Description).

Sykes differs from the instant methods by not describing the anti-CD3 immunotoxins encompassed by the claimed methods.

Gray et al. teach the use of CTLA-4 Ig fusion proteins for downregulating immune responses by inducing non-responsiveness (or tolerance or anergy), including in human transplantation (e.g. heart, liver, kidney) on column 21, paragraph 1),

including in combination with agents that inhibit T cells or induce general immunosuppression such as cyclosporine or FK506 (e.g. see columns 22, paragraphs 1-2) (see entire document, including Uses of CTLA4-Immunoglobulin Fusion Proteins Having Reduced IgG Region-Mediated Biological Effector Functions on columns 21-23).

Here, treatment can occur prior, during and post transplantation is described and therapeutic dosing regimens can be adjusted to provide the optimum therapeutic responses (see Compositions of CTLA4-Immunoglobulin Fusion Proteins on columns 19-21).

Gray et al. and Sykes differ from the instant methods by not describing the anti-CD3 immunotoxins as a means to reduce or inhibit T cell responses in transplantation immunosuppressive regimens, encompassed by the claimed methods.

In describing therapeutic approaches to organ transplantation, (see entire document), Strom note the known multi-tiered approach to immunosuppressive therapy in that several agents are used simultaneously, each of which is reacted at a different molecular target within the graft response and achieving additive-synergistic effects through application of each agent at a relatively low dose, thereby limiting the toxicity of each individual agents while increasing the total immunosuppressive effects (see page 451, column 1, paragraph 1). Strom concludes by anticipating that in the near future, antibodies and fusion proteins that target discrete steps in antigen recognition, signal transduction and effector immunity will be applied clinically.

The prior art is consistent with the known multi-tiered approach of targeting discrete steps in antigen recognition, signal transduction and effector immunity taught by the referenced methods of administering anti-CD3 immunotoxins (e.g., claims 6-10) and/or CTLA4Ig (e.g., claims 21-22) in combination with traditional or standard immunosuppressive therapy (e.g., claims 23-26, 27-28) associated with preventing chronic rejection of a transplant (e.g., claims 2-5, 11-13).

Therefore, it would have obvious to a person of ordinary skill in the art at the time the invention was made to combine the teachings of the references to reduce or eliminate T cell responses via a multitiered approach by combining anti-T cell immunotherapy, such as the anti-CD3 immuntoxins, taught by Neville et al., with a costimulatory inhibitor such as CTLA4Ig, as taught by Sykes and Gray et al., in order to target different targets and mechanisms of action to increase immunosuppresssion while decreasing the undesirable effects of immunosuppression therapy, including that which accompanies transplantation.

As pointed out above, each of the references describe the known use of combination therapy, including combination therapy that targets T cells and eliminates or reduces the number or the function of T cells in combination with other immunosuppressive agents that have different targets and mechanisms of actions associated with achieving the desired immunosuppression and promotion of long term graft survival. As pointed out above, the references describe the use of either anti-CD3 immunotoxins or CTLA4 immunosuppressive agents in terms consistent with the advantages of the combination therapy of addressing different targets and mechanisms of action in efforts to increase safety and to decrease known toxic or side-effects of immunosuppression regimens at the time the invention was made.

From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

For examination purposes, "a method of preventing chronic rejection of a transplant" is read on broadly encompassing preventing the clinical signs and symptoms disclosed on pages 5-6 of the instant specification by administering effective amounts of antagonistic anti-CD3 immunotoxins and CTLA4 consistent with standard or traditional modes of transplantation immunosuppressive recognized and practiced by the ordinary artisan regimens at the time the invention was made.

Here, the prior art teaches and the instant methods encompass
the same patient populations who are being treated with same immunosuppressive regimens to achieve the same clinical endpoints at the same intervals based upon the needs of the patient,
whether or not the patients necessarily experienced long term immunological non-responsiveness or tolerance.

Applicant's arguments have not been found persuasive.

6. No claim is allowed.

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

PHILLIP GAMBEL

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September 12, 2005